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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/809,250	03/25/2004	Heinz-Gerd Klaes	1/1477	6931

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EXAMINER	
KHARE, DEVESH	
ART UNIT	PAPER NUMBER
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/809,250	KLAES ET AL.	
	Examiner	Art Unit	
	Devesh Khare	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *20-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 39-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date ~~2/18/2005~~. 12/17/2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's election of the claims of Group I corresponding to claims 1-19 and 39-51 in the reply filed on 09/18/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 20-38 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected subject matter.

An action on the merits of claims 1-19 and 39-51 is contained herein below.

35 U.S.C. 112, first paragraph rejection

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-19 and 39-51 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions and kits useful for treating HIV wherein the pharmaceutical composition comprises nevirapine and at least one antiviral active nucleoside of formula (I) or a pharmaceutically acceptable salt or prodrug thereof does not reasonably provide enablement for pharmaceutical compositions and kits useful for the treatment or prophylaxis of viral infections broadly. The specification does not enable any person skilled in the art to which it pertains , or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors regarding undue experimentation have been summarized in *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

(1) The quantity of experimentation necessary (time and expense);

(2) The amount of direction or guidance presented;

(3) The presence or absence of working examples of the invention;

(4) The nature of the invention;

(5) The state of the prior art;

(6) The predictability or unpredictability of the art;

(7) The breadth of the claims; and

(8) The relative skill of those in the art.

Breath of claims

The instant claims are drawn to a pharmaceutical composition useful for the treatment or prophylaxis of viral infections comprising nevirapine and at least one

antiviral active nucleoside compound of formula (I) and a kit of parts for the prophylaxis or treatment of a viral infection in a patient comprising a first containment containing a pharmaceutical composition comprising nevirapine and at least one pharmaceutically acceptable carrier and a second containment containing a pharmaceutical composition comprising an antiviral active nucleoside compound of formula (I). One of ordinary skill in the art would not be apprised of the metes and bounds of compounds of formula (I) in the absence of a chemical name or distinctly set forth chemical structure.

Nature of Invention

The invention relates to pharmaceutical compositions and methods useful for the treatment or prophylaxis of viral infections.

State of the Prior Art

Hirschman US 2001/0036920 A1 is representative of the prior art at the time of the invention. Hirschman teaches that the treatment of viral diseases in humans is a major focus of medical science (page 1). While some progress has been made, viral infections are still among the diseases most difficult to treat. Despite growing understanding of viral diseases along with improved techniques for detecting and treating them, few antiviral drugs have proved effective. Further, new viral diseases constantly appear as an inevitable consequence of evolution. Thus, searching for a novel and effective way of treating viral diseases remains imperative and challenging. In developing an antiviral agent , it is well known that inhibitory activity of an antiviral agent against a particular virus cannot be equated with its inhibitory effect against another virus. For example, acyclovir has proved to be specifically effective against herpes simplex 1 and 2 but not

against cytomegalovirus (CMV), even both HSV and CMV belong to the same herpesvirus family, sharing certain genetic features. Without the knowledge of a virus' genetic traits and the chemical properties of an antiviral agent, treatment of a viral infection becomes unpredictable.

Level of Ordinary Skill in the Art

The level of ordinary skill in the art is seen to be a M.D. experienced in the treatment of viral infections or a Ph.D in the field of biomedical research.

Level of Predictability in the Art/Amount of Direction Provided by the Inventor

Please note that a single embodiment may provide broad enablement in cases involving predictable factors, but more is required in cases involving unpredictable factors, such as chemical or physiological activity, see *Ex. Parte Hitzeman,* 9 USPQ2d 1821. In the instant case, no experimental data or citations of relevant prior art are presented in support of applicant's assertion that the treatment or prophylaxis of the vast number of viral infections is accomplished by administering a patient nevirapine and at least one compound of formula (I). The prior art (Hirschman) discloses that without the knowledge of a virus' genetic traits and the chemical properties of an antiviral agent, treatment of a viral infection becomes unpredictable. Additionally, the instant specification provides no guidance as to how the skilled artisan would address various factors of concurrent co-administration of nevirapine and at least one antiviral active compound of formula (I).

Such factors include but are not limited to:

1. determination of the effects of the combination of drugs as they relate to their collective primary action chemically.

2. determination of the chemical properties of the combination of drugs (e.g., regarding collective interaction with cell receptors, toxicity, absorption), and

3. determination of the physical or structure-activity relationship between the combination of the active ingredients including cellular sites of drug action and modification of the active ingredients.

Working Examples

There are no working examples in the instant specification.

Quantity of Experimentaion Needed to make and/or use the Invention Based on the Content of the Disclosure

When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. In the instant case, the phrase "for treatment or prophylaxis of viral infections" limits the composition/kit. There are no teachings in the prior art suggesting the broad treatment or prophylaxis of viral infections using a single composition of particular treatment regimen. Applicant has not provided any working examples. As such, a skilled artisan would not recognize that a combination of nevirapine and a compound of formula (I) is useful in the treatment or prophylaxis of viral infections as broadly claimed.

35 U.S.C. 112, second paragraph rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 and 39-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(1) The chemical structure representing compounds of formula (I) is indefinite. The structure contains bonds connected to the ribose ring; however, it is unclear what atoms or moieties are connected to the other end of the bond. One of ordinary skill in the art would not be apprised as to whether applicant intends the absent moieties to be limited to H or a methyl group or if applicant intends that a limitless number of moieties are suitable.

(2) Claims 4 and 42 recites the limitation "wherein the compound of formula (I) is 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine." There is insufficient antecedent basis for this limitation in the claim. The independent claim limits the 5-position to a hydroxyl group.

(3). Claim 19 is indefinite because the following terms are not defined in claim or the specification:

"PA-457"; "KPC-2"; and "HGTV-43"; "GW-695634....., and YM-215389".

There is nothing inherently wrong with defining some part of an invention in functional terms; however, a functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the

pertinent art in the context in which it is used. Functional descriptions of chemical compounds/compositions must be coupled with a known or disclosed correlation between function and structure.

Claims which depend from an indefinite claim which fail to obviate the indefiniteness of the claim from which they depend are also seen to be indefinite and are also rejected for the reasons set forth supra.

35 U.S.C. 103(a) rejection

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

Claims 1-19 and 39-51 are rejected under 35 U.S.C. 103(a) as being obvious over Otto et al. (Otto) (US 6,949,522) in combination with Zhou et al. (Zhou) (US 6,458,772) ; Simoneau et al. (Simoneau) (US 6,806,265); and Rodgers et al. (Rodgers) (US 6,462,037).

It is noted that the "composition useful for the treatment or prophylaxis of viral infections" is claimed in the preamble of independent claims 1 and 39. In a composition claim, the intended use of the composition does not have any patentable weight towards the claimed composition.

Otto teaches the compositions of β-halonucleosides and their use in the treatment of HIV (abstract) and compounds such as nevirapine that can be administered with said

nucleoside compounds (col.33, lines 18-19) because the efficacy of a drug against HIV infection can be prolonged, augmented, or restored by administering the compound in combination with a second, and perhaps third, antiviral compound that induces a different mutation form that caused by the principle drug (col.31, lines 46-51). Otto discloses nucleoside compounds similar to instant formula (I), see formula (V) (col.10) wherein base can be pyrimidine , purine including thymine or a pharmaceutically acceptable salt or prodrug thereof. Furthermore, the bases such as thymine, cytosine, halopurine, adenine, 2,6-diaminopurine are also disclosed (col.25, lines 48-67). Otto discloses pharmaceutical acceptable salt or prodrug (col.26, lines 47-58). Otto discloses the use of other antiviral agents such as a reverse transciptase inhibitor (RTI) which can be a synthetic nucleoside (NRTI) or a non-nucleoside compound (NNRTI); a protease inhibitor; a pyrophospahe analog or a fusion binding inhibitor (col.31, lines 58-65). Otto's antiviral composition discloses specifically the combination of halonucleosides and nevirapine, however the prior art is silent in disclosing the presence of other antiviral agents including guanosine derivatives of claims 3,4,41 and 42 and a kit thereof.

Zhou teaches antiviral compounds and prodrugs 2',3'-dideoxy fluoroguanosine; 3'-flurorothymidine (col.1, line 40); and 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine (col.4, line 64) and their pharmaceutically acceptable salts. Zhou also discloses that said compounds can be co-administered with other antviral compounds such as niveirapine; delaviridine in a molar ratio of 100:1 to 1:100 especially 25:1 to 1:25 (col.16, lines 1-5). With regard to the synergistic ratio of instant claim 5, it

would be within the scope of the artisan in this art to optimize the amounts of said ingredients in the synergistic ratio through the teachings of Zhao.

Simoneau teaches the salts and prodrugs of non-nucleoside reverse transcriptase inhibitors, the close structural analogs of niverapine (abstract). Simoneau discloses that said inhibitors can be used in combination with other antiviral agents such as nucleoside/nucleotide reverse transcriptase inhibitors (such as AZT); nevirapine; protease inhibitors; viral fusion inhibitors; CCR5 antagonist; CXCR4 antagonists; integrase inhibitors; TAT inhibitors; other investigational drugs such as TMC-114; antifungal and antibacterial agents; and immunomodulating agents (col.12, lines 30-42).

Rodgers teaches the close structural analogs of nevirapine their pharmaceutical compositions and diagnostic kits for treating viral infection or as an assay standard or reagent (abstract). Rodgers also discloses antiviral agents such as delavirdine, efavirenz and nevirapine (col.13, line 47). Furthermore, Rodger teaches the pharmaceutical kit can comprise two components (a) and (b) wherein (a) and (b) can have different antiviral agents (col.47, lines 50-55 and col.49, lines 40-60). Rodgers also discloses the use of a pharmaceutical carrier and instructions (col.49, lines 55-60).

It would have been obvious to person having ordinary skill in the art at the time the invention was made, to use the pharmaceutical compositions and a kit thereof of Otto; Zhou; Simoneau; and Rodgers to treat viral infections because Otto; Zhou; Simoneau; and Rodgers references disclose that nucleoside compound of formula (I) and

nevirapine are known to be used for the same method that is being claimed as an intended use. The motivation is provided by Otto, the prior art suggests the compositions of β-halonucleosides and other antiviral agents such as nevirapine can be administered together because the efficacy of a drug against HIV infection can be prolonged, augmented, or restored by administering the compound in combination with a second, and perhaps third, antiviral compound that induces a different mutation form that caused by the principle drug (col.31, lines 46-51).

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form third composition to be used for the very same purpose....[T]he idea of combining them flows logically from their having been individually taught in the prior art (*In re Kerkhoven,* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Any inquiry concerning this communication or earlier communications from the

Examiner should be directed to Devesh Khare whose telephone number is (571)272-0653. The examiner can normally be reached on Monday to Friday from 8:00 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang, Supervisory Patent Examiner, Art Unit 1623 can be reached at (571)272-0627. The official fax phone numbers for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Devesh Khare, Ph.D.,J.D.
Art Unit 1623

November 29, 2006